

# BRIEF COMMUNICATION

## Cancer Death Rates Associated With Human Immunodeficiency Virus Infection in the United States

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Studies (1–8) of the effect of human immunodeficiency virus (HIV) infection on cancer incidence rates have all shown that rates of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) are greatly increased among persons infected with HIV but have had conflicting results concerning other cancers. Analysis of death rates offers another way to investigate the spectrum of cancers associated with HIV infection.

The National Center for Health Statistics compiles data from all death certificates of U.S. residents annually. We selected death certificates from 1990 through 1995 with any mention of cancer, regardless of whether cancer was reported as the underlying cause of death (9). We analyzed 28 categories of cancer based on all codes for cancers in the International Classification of Diseases, 9th revision (10). Supplemental codes for HIV infection identified cancer deaths with HIV infection as a concurrent cause of death (11). We limited our analysis to persons aged 25–44 years, a group in which HIV infection had become the leading cause of death (11) but in which the death rate from cancers had been relatively low before the HIV epidemic.

To obtain denominators for death rates among HIV-infected persons, we used published "plausible ranges" of the number of HIV-infected adults and adolescents in the United States at the end of 1992 (12). To reduce the likelihood of spurious associations, we used the upper bounds of these estimates to

minimize the death rates among HIV-infected persons: 675 000 males and 155 000 females. On the basis of acquired immunodeficiency syndrome (AIDS) reports, we calculated 77% were aged 25–44 years: approximately 525 000 men and 120 000 women. We estimated person-years at risk during the 6-year period from 1990 through 1995 by multiplying the 1992 estimates of the HIV-infected populations by 6, yielding 3 150 000 person-years for men and 720 000 person-years for women. To obtain person-years for uninfected men and women in the same age group, we subtracted the person-years for HIV-infected men and women from the sum of estimates of the general population for each year provided by the U.S. Bureau of the Census.

For each cancer category, we calculated death rates per 100 000 person-years among the HIV-infected and uninfected men and women. We directly standardized death rates to the age and racial/ethnic distribution of the 1992 U.S. population, assuming that the distribution of the HIV-infected population was the same as that of persons reported with AIDS. Confidence intervals (CIs) for relative risks (RRs) (ratios of the rate among the HIV-infected to the rate among the uninfected) were approximated by the first-order Taylor series method, except those for RRs of zero, which were computed by an exact method (13,14). To reduce the chance of false associations, we used 99% instead of 95% CIs for the RRs.

We found that 22 275 persons 25–44 years old died with both cancer and HIV infection reported on their death certificates from 1990 through 1995. Of these, 55.1% had KS and 38.0% had NHL, including 2.3% with both KS and NHL. RRs associated with HIV infection exceeded 1.0 (equivalent to a two-sided test of statistical significance with  $P < .01$  for a 99% CI) among men for KS (1322), NHL (136), anal cancer (61), Hodgkin's disease (11), rectal cancer (6.8), testicular cancer (4.1), multiple myeloma (3.0), lung cancer (2.8), bone and connective tissue sarcoma (2.1), oral cancer (2.0), liver cancer (1.9), and leukemia (1.7), and among women for KS (555), NHL (112), laryngeal cancer (28), Hodgkin's disease (10), cervical cancer (5.5), rectal cancer (5.3), lung

cancer (4.8), uterine cancer (4.5), oral cancer (4.3), kidney and bladder cancer (2.7), and leukemia (2.4) (Table 1). Total cancer mortality was increased 32-fold among HIV-infected men and eight-fold among women; RRs for all cancers other than KS and NHL were 2.4 among men and 2.2 among women. If the lower bounds for the published estimates of HIV-infected men and women were used instead of the upper bounds, RRs exceeded 1.0 in five additional categories among men: cancer of pleura, thymus, or mediastinum (2.8); larynx (2.7); ill-defined sites (2.6); esophagus, stomach, or small intestine (1.7); and eye, brain, or other parts of the nervous system (1.5); and in one more category among women: melanoma (2.5).

Thus, although almost all cancers with which HIV-infected persons die are KS or NHL, HIV-infected persons seem to have higher rates of death with several other categories of cancer compared with uninfected persons. The RRs for some of these are less than 3, a magnitude that could largely be due to misclassification of even a small proportion of the huge number of deaths with KS or NHL. Our estimates should be considered approximate, because they were based on a series of other estimates, with compounding of uncertainty. In particular, our use of the upper bounds of published plausible ranges for the HIV-infected population probably underestimated the RRs; use of smaller estimates of the HIV-infected population would result in larger RRs.

A major limitation of our study is that it was not controlled for potentially confounding risk factors likely to be associated with cancer-causing agents other than HIV. Because some of these risk factors are probably more common among persons with HIV infection than

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See "Notes" following "References."

**Table 1.** Number of deaths, age- and race-standardized rate (per 100 000), and relative risk for death with cancer, comparing human immunodeficiency virus (HIV)-infected persons aged 25–44 years with uninfected persons in the same age group, by category of cancer and sex, 1990 through 1995

| Cancer category (ICD-9* codes)  | Sex    | No. (%†)      | Rate  | RR (99% CI)‡            |
|---|--------|---------------|-------|-------------------------|
| Lip, tongue, oral cavity, pharynx (140–149)   | Male   | 54 (3.0)      | 1.4   | 2.0 (1.4–3.0)§          |
|   | Female | 8 (1.3)       | 1.0   | 4.3 (1.7–11.1)§         |
| Esophagus, stomach, small intestine (150–152)   | Male   | 66 (1.7)      | 2.0   | 1.3 (0.9–1.8)           |
|   | Female | 10 (0.5)      | 1.2   | 1.6 (0.7–3.9)           |
| Colon (153)   | Male   | 51 (1.3)      | 1.5   | 0.9 (0.6–1.4)           |
|   | Female | 8 (0.2)       | 0.2   | 0.2 (0.0–1.2)           |
| Rectum (154.0, 154.1, 154.8)  | Male   | 75 (7.4)      | 2.6   | 6.8 (5.0–9.1)§          |
|   | Female | 8 (1.1)       | 1.5   | 5.3 (2.4–11.5)§         |
| Anus (154.2, 154.3)   | Male   | 46 (39.0)     | 1.8   | 60.7 (38.4–96.0)§       |
|   | Female | 1 (1.0)       | 0.1   | 1.6 (0.0–71.7)          |
| Liver (155.0)   | Male   | 38 (3.1)      | 0.9   | 1.9 (1.2–3.1)§          |
|   | Female | 1 (0.3)       | 0.0   | 0.2 (0.0–48.5)          |
| Gallbladder, biliary ducts, pancreas, peritoneum (155.1, 156–159)   | Male   | 35 (1.2)      | 1.2   | 1.0 (0.6–1.5)           |
|   | Female | 3 (0.2)       | 0.1   | 0.2 (0.0–2.5)           |
| Nasal cavities, middle ear, accessory sinuses (160)   | Male   | 2 (1.4)       | 0.1   | 1.6 (0.3–7.2)           |
|   | Female | 0 (0.0)       | 0.0   | 0.0 (0.0–17.0)          |
| Larynx (161)  | Male   | 17 (3.5)      | 0.4   | 2.0 (1.0–4.3)           |
|   | Female | 9 (7.2)       | 1.3   | 27.6 (11.5–66.5)§       |
| Lung, bronchus, trachea (162)   | Male   | 396 (3.8)     | 11.7  | 2.8 (2.5–3.2)§          |
|   | Female | 71 (1.0)      | 13.5  | 4.8 (3.7–6.2)§          |
| Pleura, thymus, heart, mediastinum (163–165)  | Male   | 11 (3.2)      | 0.3   | 2.1 (0.9–5.0)           |
|   | Female | 0 (0.0)       | 0.0   | 0.0 (0.0–10.2)          |
| Bone, connective, and related tissue (170–171)  | Male   | 61 (2.6)      | 2.0   | 2.1 (1.5–2.9)§          |
|   | Female | 5 (0.3)       | 1.2   | 1.7 (0.7–4.0)           |
| Melanoma (172)  | Male   | 53 (1.4)      | 2.4   | 1.6 (1.2–2.1)§          |
|   | Female | 5 (0.2)       | 1.8   | 1.8 (0.9–3.8)           |
| Kaposi's sarcoma and other skin cancers (173)   | Male   | 12 112 (93.3) | 471.1 | 1322.4 (1208.6–1447.1)§ |
|   | Female | 158 (56.8)    | 26.8  | 554.7 (411.1–748.5)§    |
| Breast (174, 175)   | Male   | 3 (3.6)       | 0.1   | 3.0 (0.7–13.2)          |
|   | Female | 38 (0.2)      | 5.3   | 0.6 (0.4–0.8)§          |
| Uterine cervix (180)  | Female | 101 (1.5)     | 14.6  | 5.5 (4.3–7.1)§          |
| Uterus other than cervix (179, 182)   | Female | 12 (1.2)      | 1.7   | 4.5 (2.1–9.4)§          |
| Other and unspecified female genitalia (181, 183, 184)  | Female | 15 (0.4)      | 2.1   | 1.3 (0.7–2.5)           |
| Testis (186)  | Male   | 49 (3.5)      | 2.3   | 4.1 (3.0–5.6)§          |
| Prostate, penis, other male genitalia (185, 187)  | Male   | 3 (1.2)       | 0.1   | 0.6 (0.1–3.8)           |
| Urinary bladder, kidney (188–189)   | Male   | 30 (1.4)      | 0.9   | 1.1 (0.6–1.7)           |
|   | Female | 4 (0.4)       | 1.2   | 2.7 (1.1–6.6)§          |
| Eye, brain, other nervous system (190–192)  | Male   | 76 (1.3)      | 2.6   | 1.1 (0.8–1.5)           |
|   | Female | 7 (0.2)       | 1.5   | 1.0 (0.5–2.1)           |
| Endocrine gland, other than gonad (193–194)   | Male   | 6 (1.5)       | 0.2   | 1.5 (0.6–3.9)           |
|   | Female | 0 (0.0)       | 0.0   | 0.0 (0.0–3.6)           |
| Ill-defined sites (195)   | Male   | 18 (3.1)      | 0.5   | 2.0 (1.0–3.9)           |
|   | Female | 7 (2.0)       | 1.3   | 9.8 (4.3–22.8)§         |
| Non-Hodgkin's lymphoma (200, 202)   | Male   | 7813 (59.6)   | 295.0 | 135.6 (129.7–141.7)§    |
|   | Female | 650 (19.0)    | 125.1 | 112.0 (101.5–123.6)§    |
| Hodgkin's disease (201)   | Male   | 280 (12.7)    | 9.0   | 11.3 (9.6–13.3)§        |
|   | Female | 27 (1.9)      | 5.4   | 9.7 (6.4–14.8)§         |
| Multiple myeloma (203)  | Male   | 26 (3.7)      | 0.8   | 3.0 (1.8–5.0)§          |
|   | Female | 1 (0.2)       | 0.0   | 0.2 (0.0–63.5)          |
| Leukemia (204–208)  | Male   | 119 (2.1)     | 3.8   | 1.7 (1.3–2.1)§          |
|   | Female | 30 (0.7)      | 4.0   | 2.4 (1.5–3.9)§          |
| Any cancer (140–208)  | Male   | 21 063 (26.0) | 798.1 | 32.4 (31.8–33.0)§       |
|   | Female | 1212 (1.6)    | 219.4 | 7.5 (7.0–8.0)§          |
| Any primary cancer other than Kaposi's sarcoma or non-Hodgkin's lymphoma (140–172, 174–195, 201, 204–208) | Male   | 1529 (3.0)    | 49.1  | 2.4 (2.2–2.6)§          |
|   | Female | 369 (0.5)     | 59.0  | 2.2 (1.9–2.5)§          |

\*ICD-9 = International Classification of Diseases, 9th revision.

†Percentage of deaths with HIV infection among all deaths with this cancer among persons in the same sex and age group.

‡RR = relative risk. CI = confidence interval. To reduce the chance of false associations, 99% CIs instead of 95% CIs for the RRs were used.

§Statistically significant ( $P < .01$ ). Determination of whether a 99% CI excludes 1.0 is equivalent to a two-sided test of significance with  $P < .01$ .

in the general population, the higher rates of death with the associated cancers may not be causally related to HIV. For example, HIV-infected persons are likely to have been exposed to sexually transmitted pathogens, such as human papillomavirus, which is etiologically related to anal and cervical cancers (15–17). Exposure to tobacco (18), alcohol (19), and illicit drugs are other potentially confounding variables that could not be controlled in our analysis.

Our findings, like those of other studies comparing cancer rates among HIV-infected and uninfected persons without controlling for potentially confounding factors (1–5), should not be accepted as sufficient evidence of a causal effect of HIV infection on cancer incidence. Regardless of whether cancers are caused by HIV, however, such analyses demonstrate higher rates of some cancers and, consequently, the need of clinicians to look for those cancers in HIV-infected patients.

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## Notes

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